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(54) Title: IMPROVING MENTAL PERFORMANCE BY INCREASING BRAIN INSULIN SENSITIVITY

(57) Abstract

Brain glucose utilization can be increased by administering an agent that improves central nervous system insulin sensivity. By improving the central nervous system insulin sensivity and increasing brain glucose utilization, age–related memory loss and dementia can be prevented and/or reduced. The improvement in brain glucose utilization is independent of treatment for Type II diabetes. Among the central nervous system insulin sensitizers that can be administered to increase brain glucose utilization are thiazolidinediones, including troglitazone, rosiglotazone and pioglitazone. Other useful compounds include oxyzolidinediones, including JPP501, and non–chiral acyclic agents, including GL 262370, and substituted 4–hydroxy–phenylalcanoic acid derivatives which are PPAR gamma receptor activators. All of these agents act on the nuclear receptor PPAR gamma. In a preferred embodiment, the agents are administered in the form of prodrugs which are designed to cross the blood brain barrier.

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INTERNATIONAL SEARCH REPORT

In. at[redacted] Application No
PCT/[redacted]99/30066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425 A61K31/44 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	COMBS, C.K. ET AL: "Inflammatory mechanisms in Alzheimer's disease: Inhibition of beta.amyloid -stimulated proinflammatory responses and neurotoxicity by PPAR.gamma agonists" THE JOURNAL OF NEUROSCIENCE, vol. 20, no. 2, 15 January 2000 (2000-01-15), pages 558-567, XP000933946 the whole document	1-30
E	WO 00 32190 A (CASE WESTERN RESERVE UNIVERSITY) 8 June 2000 (2000-06-08) the whole document	1-13,15, 18,20,23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2000	23/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mair, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 23451 A (NOVO NORDISK A/S) 27 April 2000 (2000-04-27) the whole document especially page 1, line 23	1-5,10, 11,13, 15,19, 20,23
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E	US 6 028 088 A (PERSHADSINGH ET AL) 22 February 2000 (2000-02-22) the whole document especially column 33, Table V and VI; claims 30 and 31 -/--	1-6,10, 11, 15-17, 19-23

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	KITAMURA, Y. ET AL: "Increased expression of cyclooxygenases and peroxisome proliferator-activated receptor.gamma in Alzheimer's disease brains" BIOCHEMICAL AND BIOPHYSICAL RESERACH COMMUNICATIONS, vol. 254, no. 3, 27 January 1999 (1999-01-27), pages 582-586, XP000929650 cited in the application the whole document	1-5,10, 11,13, 15,16, 19,23
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[redacted]

In at[redacted] Application No
PCT/[redacted]99/30066

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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A	GRANNEMAN, J. ET AL: "Member of the Peroxisome Proliferator-Activated Receptor family of transcription factors is differentially expressed by oligodendrocytes" JOURNAL OF NEUROSCIENCE RESEARCH, vol. 51, 1998, pages 563-573, XP000933914 cited in the application the whole document especially page 564, lefthand column, line 18-24	1-30
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5, 10,11,15-17 and 19-22 relate to compounds defined by reference to desirable characteristics or properties, e.g. "...an agent to improve insulin sensitivity in the brain." (claim 1), "...the agent activates the PPAR gamma receptor." (claim 10), an agent which "...activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor."(claim 16), "...the agent interacts with the insulin transduction process" (claim 20), "an agent to improve mental performance" (claim 21) and "cerebral enhancers" (claim 22). The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Additionally, PPAR and RxR receptors are not adequately defined in the application so it is not possible to deduce which compounds are meant to be included in the definition "activators" of RxR, PPAR gamma or PPAR alpha receptors.

Moreover, expressions such as "a thiazolidinedione", "an oxyzolidinedione", "a substituted 4-hydroxy -phenylalcanoic acid derivative", "a natural product or is derived from a natural product", "a prodrug" etc. relate to a rather elevated number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore present claims 1-22 and 23-30 relate to a use defined as "...for improving mental performance in patients having symptoms of reduced mental performance and are (sic) neither in a state of non-insulin dependent diabetes nor a state of general impaired glucose tolerance". The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the use of the claimed compounds.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in the claims and their use related to improving mental performance with due regard to the general idea underlying the application.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In a[illegible] Application No
PCT/[illegible]99/30066

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WHAT IS CLAIMED IS:

1. A method for improving mental performance in patients having symptoms of reduced mental performance and are neither in a state of non-insulin dependent diabetes nor a state of general impaired glucose tolerance, comprising administering to such a patient an effective amount of an agent to improve insulin sensitivity in the brain.

2. The method according to claim 1, wherein the agent increases glucose utilization in discrete brain areas.

3. The method according to claim 2, wherein the discrete areas are selected from the group consisting of blood brain barrier microvessels and areas in the brain associated with mental performance or memory.

4. The method according to claim 1, wherein the agent improves glucose utilization in astrocytes or glial cells.

5. A method according to claim 1, wherein the agent is selected from the group consisting of insulin sensitizers.

6. The method according to claim 5, wherein the agent is a thiazolidinedione.

7. The method according to claim 6, wherein the thiazolidinedione is selected from the group consisting of

troglitazone, rosiglitazone, pioglitazone, darglitazone and englitazone.

8. The method according to claim 5, wherein the agent is an oxyzolidinedione.

9. The method according to claim 8, wherein the agent is JTT 501.

10. The method according to claim 1, wherein the agent activates the PPAR gamma receptor.

11. The method according to claim 1, wherein the agent has agonist or partial agonist activity at the PPAR gamma receptor.

12. The method according to claim 11 wherein the agent is a substituted 4-hydroxy-phenylalcanoic acid derivative.

13. The method according to claim 11, wherein the agent is a non-thiazolidinedione, non-oxyzolidinedione.

14. The method according to claim 133 wherein the agent is GL 262570.

15. The method according to claim 1, wherein the agent selectively activates one of the sub-types of the human PPAR gamma receptor.

16. The method according to claim 1, wherein the agent activates a RxR receptor that forms a heterodimer with a PPAR gamma receptor.

17. The method according to claim 1, wherein the agent is a combination of a PPAR gamma activator and an RxR receptor activator.

18. The method according to claim 1, wherein the agent is a natural product or is derived from a natural product.

19. The method according to claim 1, wherein the agent interacts with a PPAR alpha receptor or a PPAR delta receptor.

20. The method according to claim 1, wherein the agent interacts with the insulin transduction process so that the net effect is to increase the sensitivity or responsiveness of the insulin signal.

21. The method according to claim 1, wherein the agent is administered in conjunction with at least one agent to improve mental performance.

22. The method according to claim 19, wherein the agent to improve mental performance is selected from the group consisting of carnitine, acetyl-carnitine and cerebral enhancers.

23. A method according to claim 1, wherein the patient is one with Alzheimer's Disease.

24. The method according to claim 1, wherein the agent is delivered in the form of a prodrug.

25. The method according to claim 24, wherein the agent is provided in the form of an acid addition salt.

26. The method according to claim 24, wherein agent is linked through a spacer to a dihydropyridine redox moiety.

27. The method according to claim 1, wherein the agent is delivered in a form that enables the agent to cross the blood brain barrier.

28. The method according to claim 27, wherein the agent is delivered in conjunction with an effective amount of egressin to enable delivery of the agent across the blood brain barrier.

29. The method according to claim 27, wherein the agent is formulated as a non-ionic compound.

30. The method according to claim 27, wherein the agent is delivered microencapsulated in a poly(lactide-co-glycolide) biodegradable polymer.